decision indicated that it was improper to include broad language followed by the term "such as" and then narrower language, since it is not clear if the narrower language is merely exemplary of the broader language or if it is required.

Claim 2 was canceled when this Rule 60 application was filed. New claim 48 is similar to claim 2, except that it is directed to polypeptides. Solely to expedite prosecution, the word "optionally" is not included in that new claim. The term "optionally" in claim 2 was more superfluous than indefinite since the two optional definitions for the variable R_2 were recited after the term "optionally." (R_2 is either absent or is a polypeptide which can be cleaved *in vivo*.) New claim 48 now simply lists the two optional definitions for R_2 without the word "optionally." Accordingly, applicants respectfully traverse this objection and request that it be reconsidered and withdrawn.

2. Rejection Under § 112, Second Paragraph

The Examiner rejected claim 5 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Office Action at pages 2 to 3, Item No. 2. The Examiner contends that the definitions of R_2 and R_3 are confusing. The Examiner considers that the sequence in claim 5 that follows R_3 could be construed as the definition of R_3.

Although claim 5 was canceled when this Rule 60 application was filed, applicants have added above new claim 44, which is similar to claim 5 except that it is directed to a polypeptide. Applicants respectfully assert that one skilled in the art would understand that R_2 in claim 44 is defined as a particular nucleotide sequence that comprises (1) the particular nucleotides set forth in the claim and (2) DNA in front of

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those particular nucleotides that codes for a signal peptide (which is the definition of R_3). Thus, applicant respectfully traverse this rejection and request reconsideration and withdrawal of it.

3. Rejection Under § 112, First Paragraph

The Examiner rejected claims 1, 7 to 18, and 23 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Office Action at pages 3 to 6, Item No. 3. The Examiner did not reject the claims that are actually pending in this application. To the extent it appears that the rejection may apply to the pending claims that are added above, applicants will address them. The Examiner sets forth four bases for the rejection, which are each addressed below using the lettering employed by the Examiner.

a. Fragments

The Examiner concludes that there is limited enablement for certain DNA fragments that could be used as probes. The Examiner then presents arguments concerning minimal requirements for probes and contends that the "claims read on one or up to eight nucleotides." (It is not clear why the Examiner states an upper limit of eight nucleotides, since the claims do not include such a limitation.) The Examiner contends that very short sequences used as probes are not specific.

Applicants traverse this basis for the rejection and all of the statements in it. However, this rejection appears to be directed to DNA or nucleic acid used as probe. Since none of the present claims are directed to DNA or nucleic acids, it does not

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appear that this basis for the rejection applies to any pending claims. Accordingly, applicants request that it be reconsidered and withdrawn.

b. Hybridization

The Examiner contends that claim 7 is not enabled in view of the claim language concerning a nucleic acid that hybridizes under low stringency to DNA complementary to the recited DNA sequences. The Examiner first contends that the term "low stringency" is not defined and that the specification lacks sufficient guidance, such that undue experimentation would be required. Second, the Examiner contends that low stringency produces poor matches and that the skilled artisan would not know how to use unrelated nucleic acids resulting from such poor matches.

Although claim 7 was canceled when this Rule 60 application was filed, above applicants have added new claims 46 and 66, which define the claimed polypeptide by the nucleic acid that encodes it using language similar to originally-filed claim 7.

Applicants assert that the Examiner has failed to establish that one skilled in the art would not understand what is encompassed by "low stringency" according to the claims. Although researchers may employ varying conditions, applicants assert that one skilled in the art would understand that "low stringency" conditions are those in which a positive signal is detectable above the background. Applicants assert that one skilled in the art would be able to vary conditions such as incubation temperature, salt concentration, and buffer to obtain the desired result of selecting over background. In copending application Serial No. 08/484,307, which Examiner Draper is also handling,

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9

applicants attached a copy of Shimuzu et al., PNAS USA, 80:2112-2116 (1983), which discusses the concept of low stringency hybridization (see, e.g, Shimuzu at page 2112, second column, penultimate paragraph). Applicants request that the Examiner consider Shimuzu in a reconsideration of this rejection. (If the Examiner would prefer an additional copy of Shimuzu for this application, applicants request that the Examiner call the undersigned at (202) 408-4067 prior to acting on this application.)

The Examiner's concern that unrelated nucleic acids would be encompassed by claim 7 is not founded. It should be clear that conditions in which many different unrelated sequences hybridize is not what is intended by "low stringency" conditions as set forth in claim 7. In fact, the new claims require that the hybridizing nucleic acid code for a polypeptide having the ability to bind TNF. Accordingly, unrelated polypeptides that do not have the ability to bind TNF are not encompassed by those claims.

For all of these reasons, applicants traverse this basis for the rejection.

c. Functional Derivatives

The Examiner rejects claims 13 to 16, 18, and 23 in view of the language "functional derivative" in those claims. Presently pending claims include that language, and thus, this basis for the rejection is now addressed. The Examiner contends that such claims encompass other polypeptides that have little or no structural similarity.

Solely to expedite prosecution and to make the claimed invention more clear, all of the pending claims that include the language "functional derivative" recite a functional derivative of a particularly recited sequence. Moreover, according to the

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present specification, functional derivatives encompass chemically derivatized polypeptides (see, e.g., pages 11 to 13 of the specification), rather than amino acid substitutions, deletions, or insertions. Accordingly, the Examiner's concerns about claims encompassing unrelated molecules should be moot.

To the extent the Examiner is rejecting claims that encompass variants of the particularly recited sequences, applicants traverse the rejection. The Examiner focuses solely on an alleged lack of predictability. The Examiner fails to consider the routine screening for determining whether the claimed polypeptide variants bind to TNF. The Examiner also fails to consider the high level of skill in this art. Applicants submit that the routine screening that one of skill in the art would undertake would not rise to the level of undue experimentation. It would merely require time.

The Examiner cites no authority that would support an enablement rejection based solely on a specification's failure to provide predictable results for all embodiments encompassed by the claims. In fact, the courts have repeatedly held that experimentation is permitted under 35 U.S.C. § 112, first paragraph, even in an unpredictable field. In re Angstadt, 190 U.S.P.Q. 214, 218-219 (C.C.P.A. 1976) (The court stated that to require predictability in advance is contrary to the basic policy of the Patent Act).

The burden is on the Examiner to establish a *prima facie* case that undue experimentation would be required to make and use the claimed invention. Id. Here the Examiner has not considered the routine screening that one skilled in the art could

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carry out. The Examiner concludes that undue experimentation would be required, but provides no evidence concerning the type of experimentation involved or any particular difficulties one skilled in the art would encounter in screening the claimed polypeptides for their ability to bind to TNF.

Unpredictability in advance, however, does not establish undue experimentation, since routine screening can be employed to test for binding activity of the claimed variants. Variants that bind to TNF are within the claims, and those that do not bind to TNF are not covered by the claims. Even if not predictable in advance, such routine screening renders the present claims enabled in view of the present specification. Thus, applicants traverse this basis for the rejection.

d. Alphabetical Designations

The Examiner objects to the use of alphabetical designations in certain claims and contends such claims are not enabled. Applicants respectfully traverse this basis for the rejection and all of the statements in it. However, this rejection appears to be directed to terms that were canceled when this Rule 60 application was filed and there presently are no claims that include the alphabetical designations. Thus, it does not appear that this basis for the rejection applies to any pending claims. Accordingly, applicants request that it be reconsidered and withdrawn.

Conclusion

For all of these reasons, applicants respectfully request that the rejection under § 112, first paragraph, be withdrawn.

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4. Provisional Double Patenting Rejections

Since all of the double patenting rejections in the Office Action are provisional, applicants request that the Examiner hold these rejections in abeyance until claims are otherwise indicated to be allowable. (See Office Action at pages 6 to 7, Item Nos. 4 to 5). (This rejection also appears to be directed to DNA claims, which are not pending in this application.) At that time, applicants can sort out the claims of this application and the copending application to assure that a double patenting rejection does not remain.

5. Rejection Under § 102 (a)

The Examiner rejects claims 1, 7 to 9, 11 to 16, 18, and 23 under 35 U.S.C. § 102(a) as allegedly being anticipated by Smith. Office Action at page 8, Item No. 6. The Examiner did not reject the pending claims in this rejection. To the extent it applies to the pending claims, applicants traverse this rejection. Without addressing the substantive merits of this rejection, applicants assert that the rejection under § 102(a) is improper. To be effective § 102(a) art, Smith must have been patented before applicants' invention. Smith issued on March 7, 1995, which is after the April 20, 1990, filing date of parent U.S. application Serial No. 07/511,430. Thus, applicants respectfully traverse this rejection and request that it be reconsidered and withdrawn.

6. Rejection Under § 103

The Examiner rejects claims 1 to 18 and 23 under 35 U.S.C. § 103 as allegedly being obvious over Wallach. Office Action at pages 8 to 9, Item No. 7. The Examiner admits that Wallach fails to provide any particular DNA sequence information. The

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Examiner contends, however, that Wallach's discussion of N-terminal amino acid sequence information and Wallach's general discussion of possible methods for obtaining DNA would have rendered the claimed DNA obvious. Applicants respectfully traverse this rejection since it is at odds with legal precedent that is directly on point.

Specifically, in In re Deuel, the Federal Circuit held that knowledge of a protein, even if it is partially sequenced, does not render obvious the DNA that encodes that protein, even if methods had been known to isolate DNA using amino acid sequence information. In re Deuel, 34 U.S.P.Q.2d 1210, 1215-16 (Fed. Cir. 1995). In that case, the prior art included a partial amino acid sequence and general cloning methods that allegedly could have been used to obtain the claimed DNA using the partial amino acid sequence information.

The Federal Circuit stated that "[t]he PTO's focus on known methods of potentially isolating the claimed DNA molecule is also misplaced because the claims at issue define compounds, not methods." Id. at 1215. The Court also stated that "a conceived method of preparing some undefined DNA does not define it with the precision necessary to render it obvious over the protein it encodes." Id. at 1216. Additionally, the Court held that a claim encompassing degenerate DNA sequences encoding a particular protein would not have been obvious in view of a disclosure of a partial amino acid sequence of that protein and a disclosure of methods of using partial amino acid sequence information to obtain other DNA. Id.

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In summary, the Court held that unless the structure of the DNA was disclosed, proposed methods of obtaining the DNA would not render obvious the claimed DNA. Since the DNA is required to make recombinant polypeptides as presently claimed, and the Examiner has failed to establish obviousness of that DNA, the Examiner has failed to establish obviousness of the presently claimed recombinant polypeptides. Accordingly, applicants respectfully traverse this § 103 rejection and request reconsideration and withdrawal of it.

If there are further fees due in connection with the filing of this Amendment, such as fees under 37 C.F.R. §§ 1.16 or 1.17, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested. This fee also should be charged to our Deposit Account No. 06-0916. Any overpayment may be credited to Deposit Account No. 06-0916.

Respectfully submitted,

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Date: May 14, 1997

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